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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/375,248	08/16/99	FERRELL	R 28967/35255A

EXAMINER	
SORRELL,E	
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DATE MAILED: 02/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/375,248	FERRELL ET AL.	
	Examiner	Art Unit	
	Eleanor Sorbello	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *12,13 and 22-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 14-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-11 and 14-21 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that Group I and Group IV should be examined together. This is not found persuasive because Group I is drawn to methods wherein patients are screened for the presence or absence of a mutation which increases the patient's risk of developing a lymphatic disorder; whereas Group IV is drawn to methods of treatment of hereditary lymphedema by the ex vivo administration of cells transfected with a nucleotide encoding a wild type VEGF-3; vectors and host cells comprising the VEGF-3 nucleotide sequence. Therefore, the two groups are directed to two separate inventions.

The requirement is still deemed proper and is therefore made FINAL.

2. Applicants additionally argue the restriction requirement between Groups II and III on the basis that the same claim 12, is separated out into two groups. Group II encompasses claim 12 wherein protein products are utilized for therapy, whereas, Group III encompasses claim 12 wherein gene products are utilized for therapy. The search required for protein therapy is distinct from that involving gene therapy and thus the two groups, drawn to two distinct inventions.

Applicants additionally argue the restriction requirement between Groups IV and V. Group IV is directed to a polynucleotide encoding VEGF-3 transfected into host cells for ex vivo gene therapy whereas Group V is directed to methods for identifying modulators of intracellular VEGF-3 signaling by measuring increase or decrease in

signaling in the presence or absence of a putative modulator compound. The search required for gene therapy is distinct from that involving identifying modulators and thus the two groups are drawn to two distinct inventions.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-11, 14, 15, 18, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of screening human subjects for a mutation altering the sequence or expression of any VEGFR-3 allele.

The specification however only teaches screening human subjects using one VEGFR-3 allele which encompasses mutations in 5 specified positions.

The specification does not have adequate description of the genus of alleles which comprise the whole genus of VEGFR-3. The general knowledge in the art concerning alleles does not provide any indication of how to readily identify these alleles. The one allele described does not provide description of all the species of alleles that might be encompassed in this broad claim. The specification has also not

identified any structural feature of the alleles that is common to all members of the genus or that constitues a substantial portion of the genus. Therefore, one would conclude that applicant was not in possession of all the alleles of VEGFR-3, as the claims recite " at least one VEGFR-3 allele" .

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, a method using only the VEGFR-3 allele as encoded by SEQ ID. NO:1, but containing nucleotide substitutions at specified positions, namely C3360T, G2588A, G3141C, T3150C and G3164A but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

5. Claims 1-11, 14, 15, 18, 20, 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a method of screening for an increased risk of developing a familial lymphederma, by detecting the presence of a missense mutation in the VEGFR-3 allele at the following positions: C3360T, G2588A, G3141C, T3150C and G3164A, does not reasonably provide enablement for a method of screening for an increased risk of developing any lymphatic disorder by detecting the "presence or absence" of any mutation altering the sequence or expression of at least one VEGFR-3 allele. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method of screening human patients to determine their risk of developing a lymphatic disorder by assaying the nucleic acid of the patient to determine the presence or absence of a mutation, altering the nucleotide sequence

encoding any allele of the VEGFR-3 protein and oligonucleotide probes to be used in the aforementioned method.

The specification teaches analyzing the nucleic acid sequences from patients from families having early onset lymphederma and determining by statistical analysis the specific locations which had a high probability of having a base change wherein the base change led to changes in the VEGFR-3 protein which shared the common factor of the disease, or the propensity towards the disease. The specification teaches (see Table 2, pg. 34 of the specification) the 5 positions in the VEGFR-3 gene namely in Exons 2, 3, 6, 12 and 24, the specific base changes that produce the aforesaid changes and the 5' and 3' primer sequences or probes used for the detection.

In view of the teachings in the specification and the knowledge in the art, it is not clear that the assays described are enabled for diagnosing all lymphatic disorders.

However, the claims are drawn broadly to detecting the presence or absence of a mutation in the VEGFR-3 gene, which alters the sequence or expression of any VEGFR-3 allele. The specification does not teach that a patient which does not have a mutation at that specified location has an altered sequence or altered expression of a VEGFR-3 allele. It is not clear that the absence of a mutation in the VEGFR-3 allele will confer an altered protein expression which in turn will confer the susceptibility to develop a lympatic disorder. Therefore, in the absence of results in the specification indicating that which is claimed, one would require undue experimentation to be able to determine positions on the VEGFR-3 allele wherein the absence of a mutation will confer an altered expression of a VEGFR-3 allele.

It is well known in the art that conservative amino acid substitutions may result in altered protein phenotype and/or function. At the time of filing and subsequently thereafter, the state of the art pertaining to conservative modifications embracing amino acid substitutions, deletions, inversions, etc. of a polypeptide is unpredictable with regard to retaining the phenotype of the polypeptide or protein. For example, Ding *et al.* teaches that a single conservative amino acid substitution of alanine with isoleucine in IL-10 converts the protein to a molecule with immunostimulatory activity and that "this single conservative residue alteration significantly affects ligand affinity for receptor." (See abstract).

It would require undue experimentation to determine if the absence of a base change results in a polypeptide that would have altered properties and/or phenotype of the expressed VEGFR-3 polypeptide. The amount of experimentation required would include the trial and error determination of substitutions, deletions, inversions, etc. of single and/or multiple amino acid residues and polypeptide expression and characterization to determine whether or not the properties of the polypeptide are retained. In view of such, the invention is not enabled over the full scope as claimed.

In view of this, it would prove to be a difficult task for one skilled in the art to be able to practice the claimed invention. Hence, since one skilled in the art cannot readily anticipate the results predicted within the subject matter to which the claimed invention pertains, then there is a lack of predictability in the art.

The claims read broadly on any 6-50 nucleotides of SEQ. ID: NO: 1 of the instant application, which is 100% identical to SEQ. ID. NO: 3 of U.S. patent NO: 5,776,755,

encoding the FLT4 , a receptor tyrosine kinase, which is 4795 nucleotides long which are claimed in the instant application to be used as probes.

It is well known in the art of primer design and concepts, that specificity is generally controlled by the length of the primer and the annealing temperature of the PCR. Oligonucleotides between 18-24 bases tend to be very sequence specific if the annealing temperature is set within a few degrees of the primer T_m.

In view of the teachings in the specification and the knowledge in the art, it is not clear that one skilled in the art could, without undue experimentation select any sequence 6 nucleotides in length (and up to 50 nucleotides), having any addition, deletion or substitution which is to be used as a screening assay for detecting specific mutations in human patients for detecting an increased risk of developing a lymphatic disorder and be assured the probe selected correctly.

It is not clear that one of skill in the art could, without undue experimentation, make a kit comprising at least two oligonucleotides of the formula X_nYZ_m wherein n+m is equal or less than 5, wherein Y represents any of the 5 nucleotides A,T,G,T and U, in the absence of teachings in the specification to support such. In view of the breadth of the claims, guidance set forth, lack of working examples, the amount of experimentation required for the above is undue, and as such the claimed invention is not enabled.

Additionally, in view of the claims drawn to the detection of addition, or deletions in the VEGFR-3 gene it is not clear that the 6-mer fragments to be used for detecting 5 mutations in the VEGFR-3 allele, would infact be able to specifically detect any and all additions and deletions in the VEGFR-3 allele.

In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the amount of guidance set forth, the breadth of the claims, and the lack of working examples, one of skill in the art could not make and use the invention without undue experimentation

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-11 and 14-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 recite the phrases "correlates the increased risk of developing" or "correlating the presence of a mutation".

It is not clear what exactly is meant by the term "correlates" and needs to be replaced with a more precise term reflecting the invention per se.

The claims recite the phrase "sequence or expression".

It is not clear if applicants are referring to the mRNA sequence or the protein expressed by the mRNA or the promoter sequence. This needs to be clarified.

Claims 14-17 recite the term "wild type" human VEGFR-3 sequence.

It is not clear if there are many wild type alleles for the human VEGFR-3 sequence, in which case the specific one referred to in this specification needs to be identified.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**
>
> **(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.**

12. Claims 1, 2, 5, 6, are rejected under 35 U.S.C. 102(e) as being anticipated by Alitalo et al. (U.S. Patent. No: 6,130,071).

The claims are directed to a method of screening human subjects for an increased risk of developing a lymphatic disorder, by assaying the nucleic acid sequence of at least one of the VEGFR-3 alleles to determine the presence of a mutation. Further limitations include determining the presence or absence of a mutation altering a tyrosine kinase domain amino acid sequence of the protein encoded by the VEGFR-3 allele.

Alitalo et al. taught methods for screening for endothelial cell disorders including lymphatic vessel disorders using a nucleic acid that binds to VEGF-C. (See col. 15, lines 47-67 and col. 16, lines 1-6). The screening method comprised providing a sample of endothelial cell nucleic acids from the subject, contacting the sample of

endothelial cell nucleic acids with a polynucleotide of his invention namely mutants of VEGF-C, which hybridize to a gene encoding VEGF-C and preferably VEGF-C mRNA, determining the level of hybridization, and correlating the level of hybridization with an endothelial disorder. Alitalo et al. taught the relationship of the degree of the disorder to mutations in the tyrosine kinase receptor and provided guidance as to amounts of polypeptides of the invention that are effective in providing a biological response. (see col. 15, lines 18-20). VEGF-C is VEGFR-3. (See col. 15, lines 23 and 24).

As such, Alitalo taught all limitations encompassed by the rejected claims as argued herein.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1, 2, 5, 6, 14 and18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alitalo et al in view of Ahren, H., and Strategene.

The claims are directed to a method of screening human subjects for an increased risk of developing a lymphatic disorder, by assaying the nucleic acid sequence of at least one of the VEGFR-3 alleles to determine the presence of a mutation. Further limitations include determining the presence or absence of a mutation

altering a tyrosine kinase domain amino acid sequence of the protein encoded by the VEGFR-3 allele.

The claims are also drawn to an oligonucleotide probe comprising 6-50 nucleotides that have a sequence identical or complimentary to the wild type sequence of VEGFR-3, except for one nucleotide sequence difference. The claims are additionally drawn to kits comprising at least two oligonucleotides each at least 5 nucleotides long (and possibly upto 50), and arrays of oligonucleotide probes immobilized on a solid support.

Alitalo et al. taught methods for screening for endothelial cell disorders including lymphatic vessel disorders using a nucleic acid that binds to VEGF-C. (See col. 15, lines 47-67 and col. 16, lines 1-6). The screening method comprised providing a sample of endothelial cell nucleic acids from the subject, contacting the sample of endothelial cell nucleic acids with a polynucleotide of his invention namely mutants of VEGF-C, (VEGFR-3 is one form of VEGF-C : See col. 15, lines 23 and 24) which hybridize to a gene encoding VEGF-C and preferably VEGF-C mRNA, determining the level of hybridization, and correlating the level of hybridization with an endothelial disorder. Alitalo et al. taught the relationship of the degree of the disorder to mutations in the tyrosine kinase receptor and provided guidance as to amounts of polypeptides of the invention that are effective in providing a biological response. (see col. 15, lines 18-20).

Alitalo et al. did not teach the construction of probes and kits.

Ahren et al. however, emplasized that todays research is accomplished with kits. Therefore, as of the filing of this application, it would have been obvious to combine the teachings of Alitalo et al. with that of Ahren et al. Stratagene Inc. sell kits for the gene characterization such as for sequencing, mapping, nucleic acid hybridization etc.

Therefore it would have been *prima facie* obvious at the time the invention was made to combine the teachings of Alitalo et al. and Ahren resulting in methods for detecting polymorphisms in the VEGFR-3 allele, together with kits and probes for use in the aforementioned methods to result in the instant application.

Therefore one of ordinary skill in the art would have been motivated to combine the teachings of Alitalo et al. and Ahrens because of its potential application for the commercial purposes in medical diagnostics. One of ordinary skill in the art would have reasonably expected success in testing the efficacy of kits and probes in a method for diagnosing increased risk of developing a lymphatic disorder which would not require undue experimentation.

Therefore, claims 1 and 2, 5, 6, 14 and18-21 are rejected as being obvious.

Conclusion

15. Claims 1-11 and 14-21 are rejected.

16. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

Questions of formal matters can be directed to the patent analyst,

Tracey Johnson, whose telephone number is (703) 305-2982.

If attempts to reach the examiner by telephone are unsuccessful; the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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